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medical journal
university of toronto

january 1977

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medical journal

university of toronto

Established December 1923
An Undergraduate Publication

VOLUME LIV
NUMBER 2

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THE COVER: The series of paper dolls suggests this issue’s feature topic, pediatrics.

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For their generous financial support (with its consequent psychological boost) we would like to extend our sincere thanks to the following individuals:

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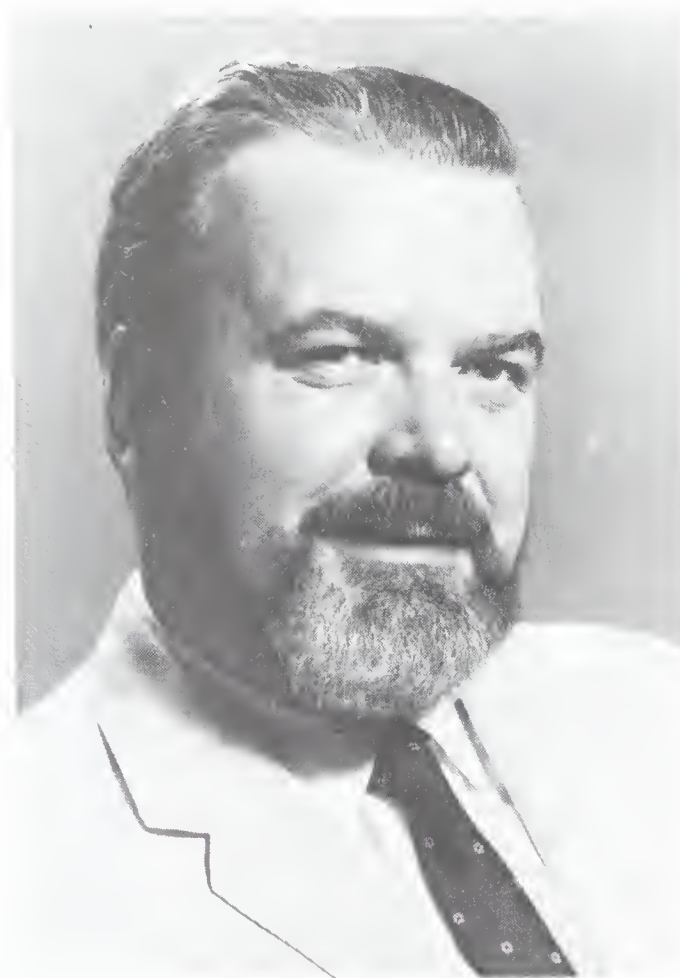
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Child Development

**Quentin Rae-Grant M.B., Ch.B., D.P.M., F.R.C.
Psych., F.R.C.P.(C)**

Dr. Rae-Grant attended the University of Aberdeen School of Medicine and graduated in 1951 receiving M.B., Ch.B. with Honours. His internship and residency were taken in Scotland and London, England.

Well experienced in the field of adult and child psychiatry, Dr. Rae-Grant has served as Director, Chief and consultant to various hospitals, associations and community centres. At present he is the Psychiatrist-in-Chief at the Hospital for Sick Children, Professor and Vice-Chairman for the Department of Psychiatry, University of Toronto, as well as being consultant to St. Michael's Hospital, Clarke Institute, and Juvenile and Family Court of Metropolitan Toronto. In addition to his practical experience, he has numerous publications on the topic of child psychiatry.



Although everyone would admit that a knowledge of normal and abnormal child development is essential for the informed practice of medicine, it is still an area of dispute, confusion, and contradictory theories showing only one common feature, namely, that the degree of conviction with which beliefs are held is an inverse proportion to the factual base from which they derive. There are a number of reasons for this.

One of the most basic is to make one's own and one's family experience of development the norm against which to measure alternatives. Where each man is his own expert, wild swings of practice can occur on seeming whim. For example, the educational field has gone from opposition to past practice, because some of its effects were negative, through a freer, more experimental approach and now back to a disillusioned attempt to return to that "which was good enough for us".

The second reason derives from the different viewpoints from which investigators have looked at this process. Thus some have emphasized cognitive and intellectual development, e.g. Piaget; others have chosen to focus on social development and the impact of culture; while others have derived their initial observations from adult memories and have tried to apply them in a retrospective fashion to children. Although all would accept that development is influenced and determined by (a) genetic endowment; (b) temperamental characteristics; (c) the experiences and happenings in early years, and (d) society's norms and expectations, it is most usual that those adopting one approach give only a cursory nod to the other areas. It is rare that a synthesis is attempted that tries to integrate these components.

A word about each of these in turn. The debate of nature versus nurture is

presently more influenced by political and social arguments and considerations than it is by evidential support. Genetic endowment sets the pattern and limits for later development. This is clear in specific areas and conditions such as Tay-Sachs, mongolism, and other specific syndromes in the area of mental retardation. But the debate rages fiercely when one moves from these obvious conditions to those of normal or above normal endowment. Despite the laudable attempts to claim that intelligence can be markedly influenced by positive environmental factors, present evidence would point to genetics determining to a great extent the potential that a person can achieve, which potential may not be realized under adverse conditions such as poor nutrition during pregnancy, difficulties during delivery, the handling of prematurity and environmental deprivation with a lack of stimulation and learning

opportunities. Repeatedly it has been demonstrated that early stimulation programs are reflected in substantial improvement on standard testing, but this does not necessarily lead to the conclusion that these by themselves in the absence of the genetic potential raise functioning capacity and competence.

Temperament has recently become respectable and recognized, thanks to the work of such investigators as Chess. The idea that the child arrived in the world mentally like an empty blackboard on which the script of life determined the outcome ignored the facts that children are born with different potentials and styles of reaction that in turn influence the way in which the environment responds to them. These characteristics are seen to remain relatively stable over a number of years.

Though much has been written with regard to the relationship of various styles of child rearing to later performance, the evidence of specifics is still tenuous. Rejection and parental neglect do have clear effects on some but not necessarily all children. Early separation, repeated separations and poor placement alternatives clearly influence the course of child and adult life. A sense of security, a welcoming home base promote but do not guarantee healthy development. Too much atten-

tion has concentrated on moving from the abnormal to the normal by inference. Too little has been given to a study of children who go through similar experiences without experiencing such personality and emotional disturbances.

At the moment this is an expanding and increasingly exciting area. The instruments and units of observation have become much more discreet where before they were global. Studies of early mother/child bonding are now by direct observation of the action not only of the mother on the child but on the converse as well. Increasing attention is being given to the changes in medical practice, the consequent long term survival and its impact on children and on those who have to care for them.

Genetic detection and counseling are developing rapidly, but only tentatively are the effects of the counseling interview being evaluated. As it becomes more feasible to detect abnormal genetic potential, so the interpretation of genetic defect, the understanding of the interpretation, what is remembered of the interpretation, and the impact on the individuals being counselled will require our attention. The problems increase experientially if practice moves into the area of genetic tampering.

Clearly, many illnesses which have been regarded as environmentally and

experientially determined now seem, as the result of careful twin studies, to have a clear genetic component as part of their etiology. Schizophrenia, unipolar and bipolar depression, psychopathic behaviour and alcoholism all fall into this category, yet the appearance of these conditions or their non-appearance does seem to be influenced by the happenings of life rather than pursuing solely a pre-ordained course.

As understanding increases so does the responsibility of the medical profession to anticipate the effect of changes in medical care and the burden this may throw on family resources, to mitigate the adverse effects of environment and to concentrate, where necessary, on the prevention of neglect and of depriving experiences. As increasing knowledge provides increased specificity of how and when to intervene, so it may necessitate simultaneously that we as individuals within society look at the conditions under which children grow and develop, and advocate priority for change as a major investment in the future rather than the current erratic responses to political pressure.

The answers to some of the questions will create problems for concerned solution in individual, family, cultural and social terms. The aim is not the achievement of bland normality, but the opportunity for each individual to develop to the maximum of his or her potential.

Myocardial Infarction and Sudden Death

Frances Frankenburg 7T8 and Catherine Zahr 7T8

Sudden death frequently occurs with or shortly after a myocardial infarction. In this paper the sudden death of a diabetic man who had suffered a myocardial infarction will be discussed.

Clinical Presentation

Mr. A. L., a 68-year-old male, presented to the hospital emergency department on July 14, 1976, with a 10-day history of intermittent precordial pain of pressing nature which radiated down his left arm. The pain was accentuated by moving or bending, lasted five to 15 minutes, and was unrelieved by rest. Diffuse tenderness over the left

precordium was presented. He denied previous episodes of chest pain or other medical problems. He had been treated for hypertension with propranolol (20 mg q6h) and hydrochlorothiazide (100 mg qd) since 1973. An electrocardiogram in September, 1973, was within normal limits. In addition he had diabetes mellitus of 10 years which was controlled with tolbutamide (500 mg bid).

On admission, physical examination revealed an alert male in no distress. Blood pressure was 160/90 mm Hg, pulse 88 per minute with a heart rate 140 per minute on the monitor, and respirations 24 per minute. The chest was clear. Heart sounds were normal

and the rhythm was irregularly irregular. Jugular venous pressure was 3 cm above the sternal angle. The remainder of the physical examination was unremarkable.

Laboratory Examination

Upon admission blood glucose was 428 mg% (normal fasting glucose 65–110 mg%), BUN (Blood Urea Nitrogen) 23 mg% (N: 10–20 mg%), serum electrolytes within normal limits, hemoglobin 14.9 g/100 ml (N: 13.5–17 g/100 ml), platelet estimation normal, WBC 11,000/mm³ (N: 4,000–11,000/mm³). Blood gases on room air were

pH 7.47 (N: 7.36–7.42), $p\text{CO}_2$ 41 mm Hg (N:36–44 mm Hg), $p\text{O}_2$ 68 mm Hg (N: 100 minus age/5 mm Hg). SGOT (Serum Glutamic Oxalacetic Transaminase) was 20 units (N: 10–45), LDH (Lactic Dehydrogenase) 774 units (N: 130–350), and CPK (Creatine Phosphokinase) 50 units (N:5–45). A chest X-ray did not show evidence of congestive heart failure. An electrocardiogram revealed an irregular rhythm with atrial fibrillation and multifocal ventricular premature beats (many three in a row, more than 15 per minute), and ST segment elevations in leads V1–VH.

A clinical diagnosis of acute myocardial infarction with possible pericarditis was made, and he was admitted to the coronary care unit. He was treated with xylocaine intravenous drip (4 mg/min) which eliminated the ventricular beats, and digoxin (.25 mg p.o.) which controlled the ventricular rate during atrial fibrillation. Tolbutamide therapy (500 mg bid) was continued.

CPK and SGOT levels decreased, but remained within normal limits. LDH fell from 774 units on July 14 to 576 units on July 16. Except for an inability to control his blood sugar, recovery was uneventful.

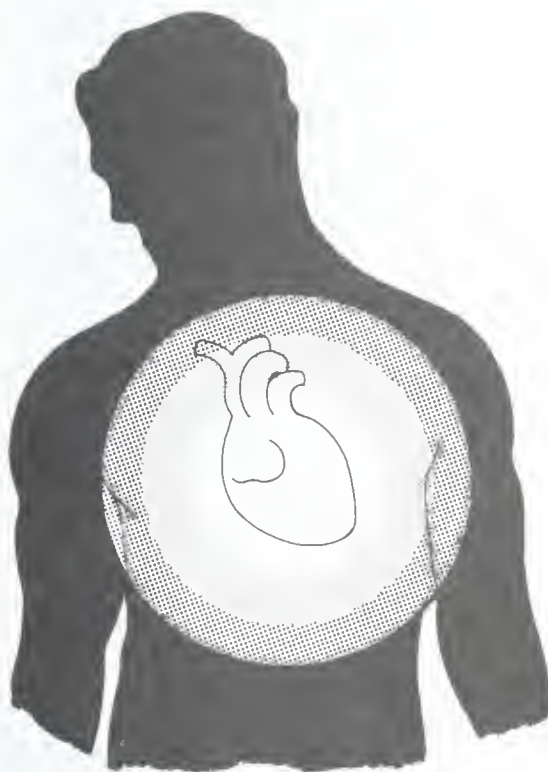
On July 19, the xylocaine drip was replaced by quinidine (200 mg p.o. 96h), digoxin was discontinued, and he was transferred from the coronary care unit to a convalescent unit. While awaiting discharge, quinidine and tolbutamide were continued. On July 22, while speaking to his physician, the patient collapsed. He was unconscious and pulse and blood pressure were unobtainable. Despite resuscitation procedures, there was no spontaneous respiration or pulse, and the patient died.

Clinical Discussion

Myocardial ischemia must always be included in the differential diagnosis of chest pain occurring in a middle-aged or elderly man. A careful history and physical examination, together with EKG, chest X-ray and other laboratory studies may not be sufficient to make the diagnosis certain. If myocardial ischemia is strongly suspected and cannot be excluded, treatment proceeds as though it were present.

The history in this case is suggestive but not typical of angina pectoris. The spatial, temporal and qualitative description of the pain and background of high blood pressure and diabetes mellitus all point to a diagnosis of ischemic heart disease. The exacerbation by movement however suggests pleural, pericardial or musculoskeletal origin or involvement.

Physical examination is usually not helpful in making the diagnosis. Even if there are clear signs of musculoskeletal abnormalities, concomitant myocardial ischemia cannot be ruled out. Angina pectoris is not commonly associated with physical signs. People experiencing a myocardial infarction are commonly pale, anxious and distressed, but at least 15 to 20 per cent of myocardial infarctions are painless (Wintrobe, 1974). The incidence is higher in the elderly and the diabetic. After a myocardial infarction heart sounds tend to be quiet; there may be an atrial gallop sound (S4) or a paradoxical left parasternal pulsation. Blood pressure and heart rate may be increased, normal or de-



creased. Mr. L's precordial findings cannot rule out either angina or myocardial infarction. The absence of a rub cannot rule out pericarditis; the rub is frequently transitory.

On the basis of history and physical examination, then, angina pectoris, possibly with one or more myocardial infarctions, must be suspected. The exacerbation of pain by movement suggests that pericarditis a frequent complication of myocardial infarction, could also be present.

Laboratory results can confirm the clinical diagnosis if they show the characteristic findings associated with ischemia, but they cannot exclude the diagnosis. Nonspecific signs of tissue necrosis are leukocytosis persisting three to seven days after an infarct, and

an elevated erythrocyte sedimentation rate which persists for several weeks. Serum enzymes are also elevated—particularly serum glutamic oxalacetic transaminase (SGOT), a creatine phosphokinase (CPK), and lactic dehydrogenase (LDH).

The borderline degree of leukocytosis and low arterial oxygen tension are compatible with myocardial injury. The SGOT level is normal, CPK slightly raised, and LDH markedly raised. Since raised LDH levels persist for 10–14 days after an infarction while SGOT and CPK return to normal levels by the fifth post-infarction day, the serum enzyme levels reflect an infarction occurring one to two weeks prior to admission.

Raised LDH Levels are however not specific for myocardial infarctions; they are also raised in pulmonary infarctions, carcinomas and anemias. There are five isoenzymes of LDH which are distributed in varying proportions in different body tissues and which can be distinguished by starch-gel electrophoresis. The most rapidly migrating isoenzyme—LDH-1, predominates in cardiac muscle. If the laboratory is equipped to separate the isoenzymes, and finds a raised LDH-1, this is a specific indication of myocardial injury.¹⁴ The subsequent decrease in the three enzyme levels fits in well with a diagnosis of previous myocardial injury.

The electrocardiographic manifestations of ST segment elevation in chest, leads V_1 – V_4 are specific after an acute anteroseptal myocardial ischaemia. The confinement of the elevation to the right anterior chest leads suggests that there is no associated acute pericarditis.¹⁴

The arrhythmias are typical of myocardial infarction. Atrial fibrillation occurs in 6–13% of patients following myocardial infarction, and ventricular premature beats are the most common arrhythmias during the infarction.⁸

The absence of ECG findings can never be used to exclude the possibility of a myocardial infarction if it is suggested by the history and physical examination as the ECG changes do not always develop immediately. In this case the ECG findings were diagnostic of myocardial infarction. The serum enzyme changes though were characteristic of an older injury.

Sudden death following an acute myocardial infarction most frequently occurs within the first hour, 40–75% of deaths occurring within this time period.⁶ These deaths are due primarily to serious arrhythmias secondary to myocardial ischemia which compromise the integrity of the heart as a pump. Early hospitalization or prehos-

pital treatment of patients with acute myocardial infarction is necessary to prevent and correct life threatening arrhythmias, subsequent shock, and death.⁹ Pump failure occurring in this period is an incompletely understood phenomenon, particularly when the size of the infarction is small. Since the mortality rate due to arrhythmias has been reduced. Shock accounts for 50% of deaths in patients with myocardial infarction.¹⁴

A patient who survives the acute phase of a myocardial infarction may collapse suddenly during an otherwise uneventful convalescence. The differential diagnosis includes another myocardial infarction complicated by an arrhythmia or pump failure, septal perforation, papillary muscle rupture, or ventricular aneurysm with left ventricular failure, ventricular rupture and subsequent tamponade. Prompt clinical examination and evaluation of the patient may suggest one of the above problems, and will guide further investigation as well as immediate treatment.

The unexpected development of left ventricular failure and pulmonary edema accompanied by the appearance of a pansystolic murmur is indicative of septal perforation or mitral regurgitation secondary to papillary muscle rupture. The additional strain superimposed upon a damaged ventricle can cause sudden decompensation. It may be impossible to differentiate the two conditions without demonstrating the presence or absence of left to right shunting by cardiac catheterization. Dysfunction of papillary muscle may cause the apical systolic murmur of mitral regurgitation in 50% of patients with myocardial infarction, but very few suffer major hemodynamic consequences. Surgical treatment consisting of mitral valve replacement or septal repair may bring about dramatic improvement if the patient can withstand the stress of surgery (Walton).

Ventricular aneurysm, occurring in 10-20% of myocardial infarction survivors, may cause death in the convalescent period and is associated with left ventricular failure, sudden ventricular arrhythmia, or major embolic phenomena. An abnormal cardiac silhouette may be seen on X-ray. Diagnosis is based upon coronary arteriography and left ventriculography. Surgical excision may be indicated.¹³

Clinically, with rupture of the ventricular wall, the patient may be improving when he suddenly collapses and loses consciousness. Blood pressure and pulse are unobtainable, jugular venous pressure is elevated, and resuscitation measures with closed cardiac massage

are not successful. An electrocardiogram may show normal sinus rhythm, but with each contraction blood is pumped into the pericardium compressing the heart and leading to cardiac tamponade. The normal pericardium is not easily distended and can accommodate only 100 to 150 mls. of blood. As the intrapericardial pressure rises, cardiac output decreases. Tamponade must be considered when arterial blood pressure decreases and there is evidence of venous hypertension.

Rapid diagnosis followed by prompt surgical procedures such as pericardial tap, extracorporeal circulation, thoracotomy with clot evacuation, temporary closure of the rupture and later infarctectomy may on occasion save the patient's life.

Autopsy Report

Gross findings at autopsy were consistent with the clinical picture. The pericardial sac was filled with 100 ml. of blood and 250 g. of clotted blood. The pericardial surface was granular and adherent to the epicardium over the left anterior ventricle wall. In this area the epicardium was discolored and hemorrhagic. The left ventricle was hypertrophied and the heart weighed 465 g. A recent infarct was present on the anterior wall of the left ventricle extending from the apex nearly to the valve rings, posteriorly, and into the septum. The center of this focus was soft and yellow with a hemorrhagic border. Edema was present and there

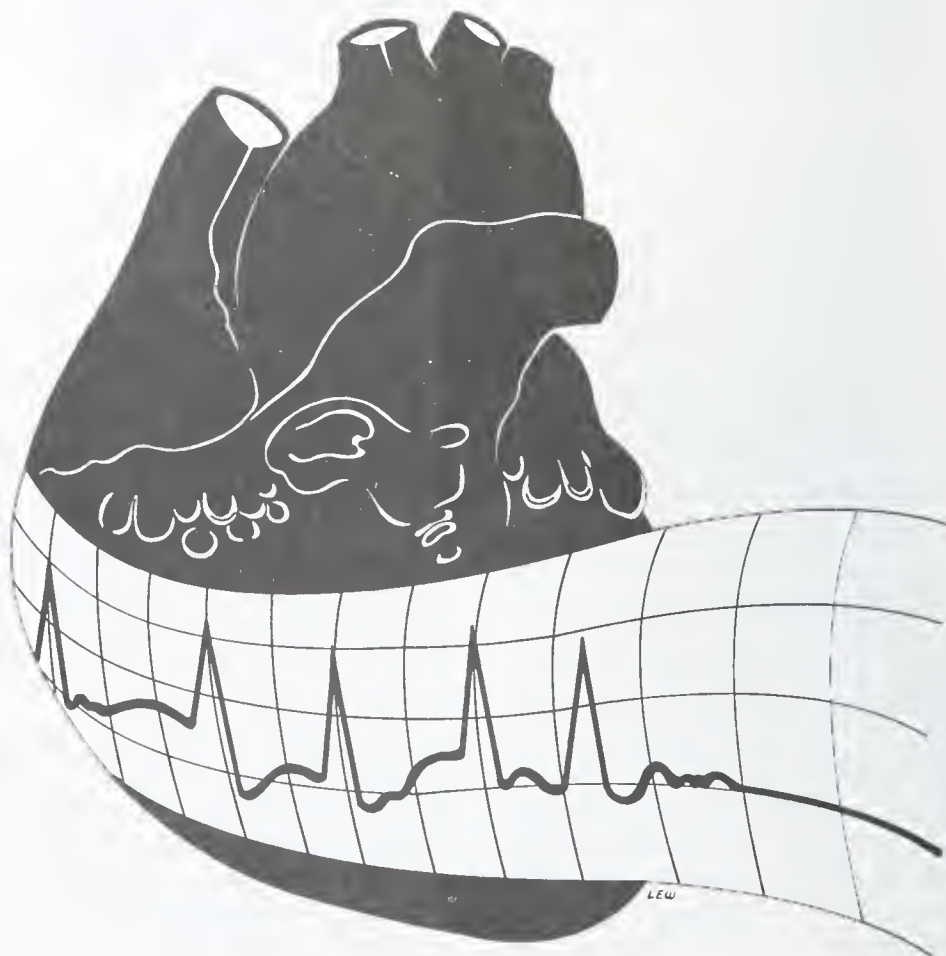
was a 0.3 cm. rupture in the anterior wall of the left ventricle and at the apex of the left ventricle. Atherosclerotic plaques and calcification involved all coronary arteries and the interventricular branch of the left was occluded by a recent laminated thrombus. The aorta was moderately atherosclerotic with atheromatous plaques and calcification with ulceration present only in the abdominal aorta below the level of the renal vessels. All branches of the aorta were mildly involved by atherosclerosis, but thrombus-free.

The spleen was reddish, soft and congested with an extensive recent infarct. A fracture of the right fifth rib with hematoma was also present.

Microscopic Findings

Right and left circumflex coronary arteries were occluded by atheromatous plaque formation with focal calcification to within 50% and 70% of their diameter respectively. Sections of the left anterior descending artery showed narrowing due to atheroma formation as well as occlusion of the lumen by a recent thrombus showing no evidence of organization.

The left ventricle contained an extensive transmural infarct which involved papillary muscle, sparing a narrow margin of muscle under the endocardium. The infarcts were of various ages, from four to eight days with extensive necrosis of muscle, neutrophilic infiltration and basophilic granules. Other areas exhibited necrosis of muscle cells surrounded by early fibrosis,



chronic inflammatory cells and hemosiderin-laden macrophages. In addition there were areas of granulation tissue formation. In the area of muscle necrosis there was rupture of the myocardium with an overlying laminated thrombus and hemorrhage into the pericardium.

Hemorrhage with acute and chronic infiltrate involved epicardium overlying the infarct and rupture site. There were numerous fibrous adhesions. Thrombus was adherent to the pericardium which also showed acute and chronic inflammatory reaction.

Discussion of Pathology

The ischemic area in the heart of a person surviving a myocardial infarction undergoes necrotizing changes which make it soft and weak in the days following the infarction. Early changes are due to the onset of coagulative necrosis, interstitial edema, and marginal neutrophilic exudation. Necrosis is progressive, and fatty change is maximal between the fifth and tenth day. The infarcted area looks yellow with hemorrhagic areas.

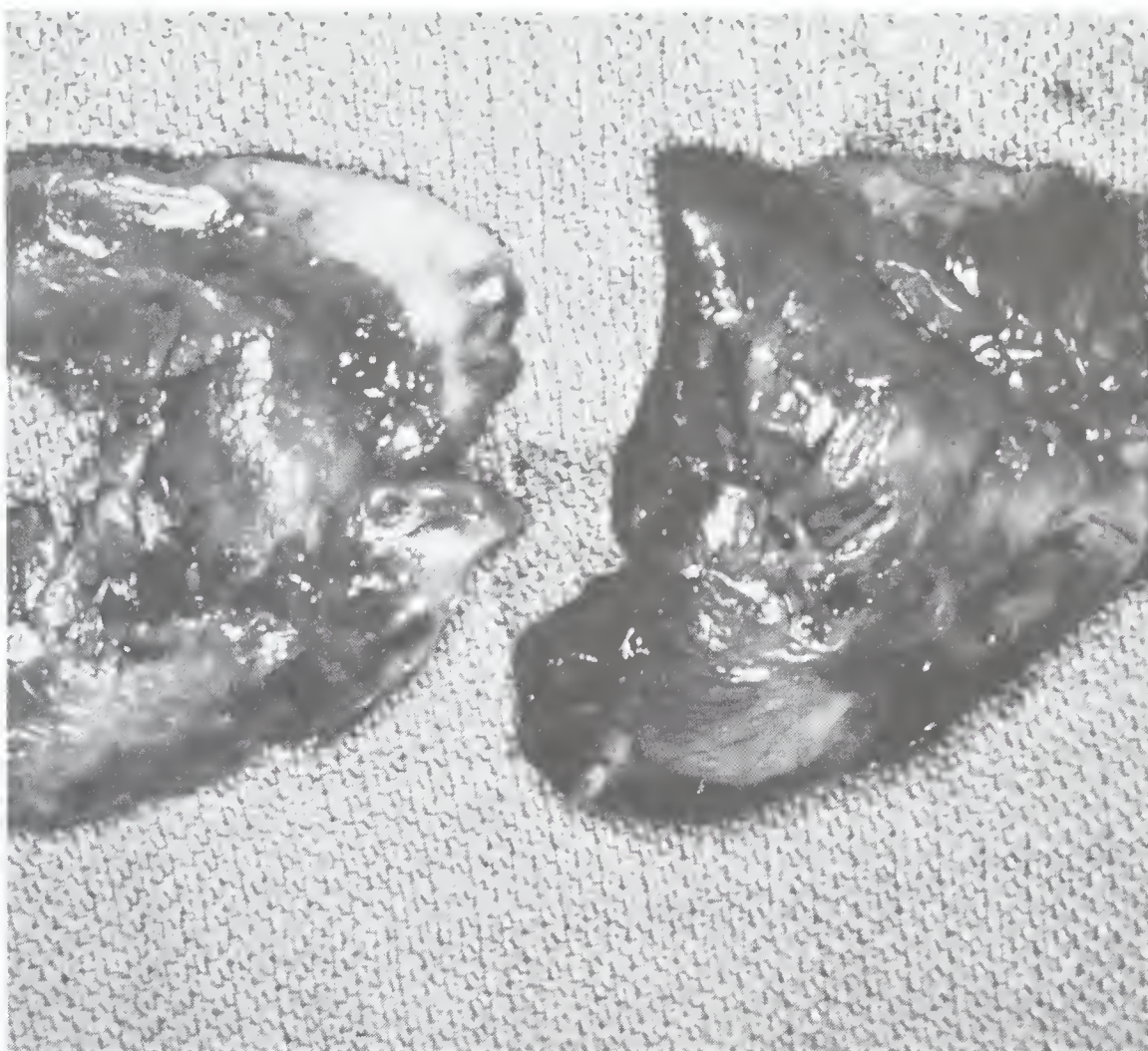
As necrosis of the damaged myocardium progresses, reparative processes also become apparent. In areas of necrotic muscle, fibrous scar tissue begins to be formed by fibroblasts five to seven days after myocardial infarction. The ingrowth of fibrous vascularized tissue is apparent upon gross examination by the tenth day.¹¹

Myocardial rupture is therefore most likely to occur towards the end of the first week following the myocardial infarction when the infarcted area is particularly soft. Inability to control the patient's activity (e.g. the psychiatric patient), increasing age, and female sex appear to be risk factors in the occurrence of rupture.⁵

In the lungs, the alveoli contained a few hemosiderin-laden macrophages and an occasional RBC. The pancreas showed fibrosis and atrophy with many foci of autolysis. In the spleen there was a recent wedge-shaped infarct surrounded by acute inflammatory cells. No thrombus or embolus was identified.

In summary, the pathological findings include:

- 1) Thrombosis of the left anterior descending coronary artery; recent infarction of the anterior wall of the left ventricle extending into the septum; rupture of myocardium with hemopericardium; mural thrombus of left ventricle; pericarditis.
- 2) Moderate atherosclerosis.
- 3) Recent splenic infarct.
- 4) Fractured right fifth rib with hematoma.



Sections of the ventricular wall showing the area of rupture.

Conclusion

The clinical history and pathological findings in this case are typical of myocardial infarction complicated by rupture of the ventricular wall and hemopericardium. This patient's myocardial infarction resulted in several other common complications including pericarditis, arrhythmias, mural thrombus, and possible embolism to the spleen. Sudden death in relation to myocardial infarction is most commonly associated with one or more of three complications: fatal arrhythmia, acute pulmonary edema, or cardiac rupture. "Rupture of the ventricular wall of the heart occurs in about 2 or 3% of cases of myocardial infarction, usually in the first week, but, since virtually all have been fatal, cardiac rupture accounts for 5 to 15% of the hospital mortality."⁴

The authors are grateful to Dr. Pritzker (Mount Sinai Hospital) and Dr. Ranganathan (St. Michael's Hospital) for their helpful criticisms. We are also grateful to Mr. Ivan Gareau of the Dept. of Instructional Media of Mount Sinai Hospital for the photograph.

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Sex and the Medico— Not Just More B.S.

Like snow in Toronto in January, it was inevitable. Seeping, slithering, sizzling from the hotbeds to the South of us, recognizing no national boundaries, the Sexual Revolution arrived, in all its torrid shame and glory (ahem). No one can say precisely when, or why, or how—nay, or even what. Not to worry, though, it doesn't really matter. Everyone *knows* it's happening; everyone with one nanogram of sensitivity has felt its presence, to a greater or lesser degree.

Here Comes the Sun

Reactions have, naturally, run the full spectrum from rave reviews through frank yawns to scorching condemnations. Typifying the first category is the belief that the sexual revolution has permitted a human revolution rivaling the Renaissance in its impact upon man's concept of the world and his place in it. It heralds the (forgive the cliché) age of aquarius where people can achieve newly expressive, creative, and loving levels of existence not possible before under the clouds of

sexual inhibitions and traditional role modeling.

Bungle in the Jungle

Conversely, we have worried people watchers quoting all those astronomical, yet familiar sounding, statistics (which apply equally as well to Canada as to the U.S.). Such as in 1975, more than a million U.S. couples divorced, twice as many as in 1966, and three times as many as in 1950. From 1970 to 1975, female heads of households rose 30%. The number of people under 35 maintaining a household alone doubled from 1.5 to 3.0 million. In 1975, kids under 18 of broken marriages numbered one million, as in each of the previous three years. There were fewer marriages in 1975 than any year since 1969. The fertility rate for women of childbearing age dropped to 1.8 births (2.1 are necessary to just replace the population). In 1960, according to the Office of Population Research at Princeton, 13% of married women aged 25-29 were childless. In 1975, it was 21%.¹ Doom impends!

Naiveté and, yes, awe have been upstaged by a precocious cynicism among the young—couples hiding their married state for financial (tax refunds, student loans), social, and 'image' reasons: discos catering to teenage homosexuals and exhibitionist odd couples and triplets, and so on and so on and so on.

Has Medical Education Caught Up With The Sexual Revolution?

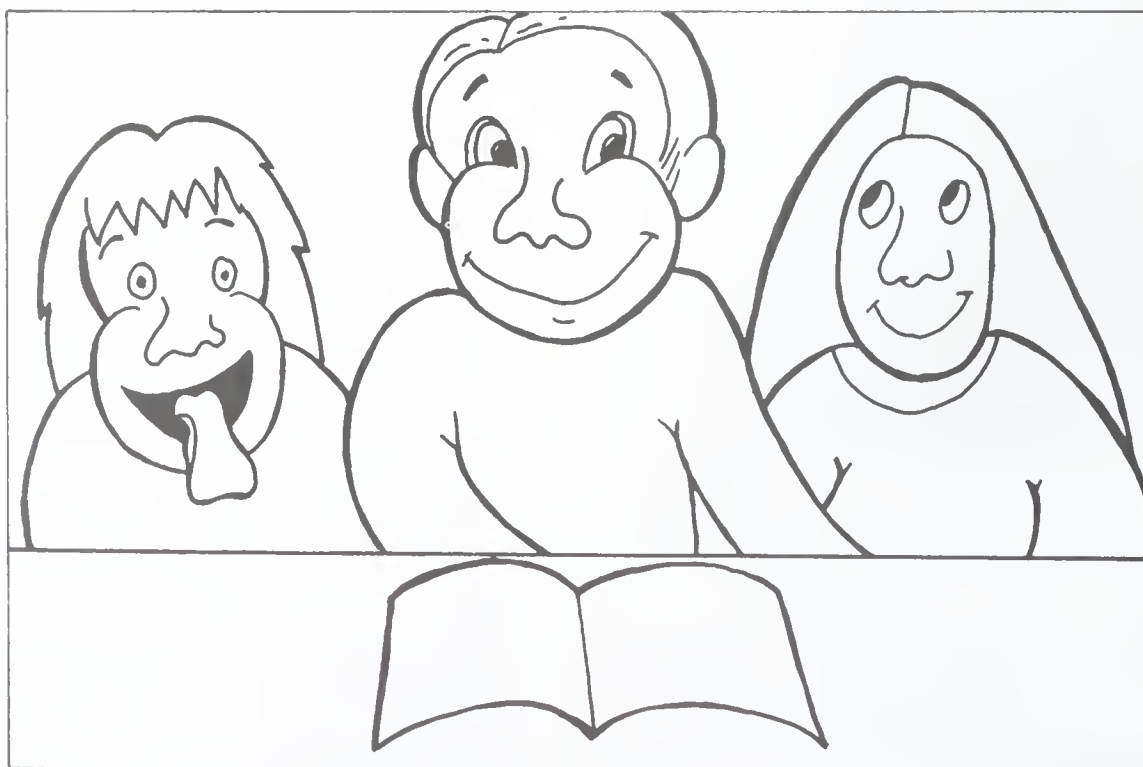
Whatever our personal opinion, we can't deny the fact that people, including doctors and patients, *have* changed, and *are* changing still. Thus acknowledging the 'facts' of the 'outside' world, we, as medical students, may legitimately wonder if the *practice* of medicine has changed at all as a result. The answer seems to be a resounding YES. It has been said that "the doctor of tomorrow will find that his patients won't shun him if he tries to tell them too much about sex: rather, they'll shun him if he doesn't help them find sexual satisfaction."²

Has the *teaching* of medicine changed at all? It was in the search for an answer to this question that I unearthed the information to follow.

"In a 1959 study, half of the graduates of Philadelphia's five medical schools said that masturbation frequently causes mental illness—and 20% of their professors agreed. Even in 1975 15% of students questioned, thought there was a connection between masturbation and mental illness."³

"In 1968, it was reported that less than 20% of the senior medical students questioned, knew what it meant when a patient said she was a practicing lesbian."⁴ Meanwhile, other data indicate that 90% of all physicians do some marital and sexual counseling—yet only 15% feel adequately trained to do so.

Spurred by such dismaying deficiencies in student and graduate knowledge of human sexuality, U.S. medical schools have responded with a battery of formal courses on the subject. Three



"Today in class we will discuss everything you've always wanted to know about sex, but were afraid to ask . . ."

schools offered courses in sexuality in 1960, 30 in 1968, and more than 100 in 1976. Already-practicing physicians also have ample opportunity to join continuing education programs in sexuality. Most notably, the Universities of Minnesota, Pennsylvania, California-San Francisco, Johns-Hopkins, and Yale offer advanced extensive programs covering everything from sexual biology and sexual dissatisfaction ('dysfunction' is passé), to sexual components of disease and varieties of sexual behavior and preferences. The Sexual Attitude Restructuring (SAR) is alive and well and living in the more avant garde American institutions. These SAR sessions, developed by the American National Sex Forum, are apparently offered at dozens of medical schools to not only medical students, but also to thousands of others including nurses, theologians, and counselors. SAR's work from the 'given' that the key to all sexuality training is in attitude. "The anxieties, prejudices and fears that plague all of us become intolerable in a physician if they impede his ability to treat a patient whose sexual practices are different from his own."⁵

Meanwhile, Back at the Ranch

The true blue Canadian reader may well protest, "But this is all *American*

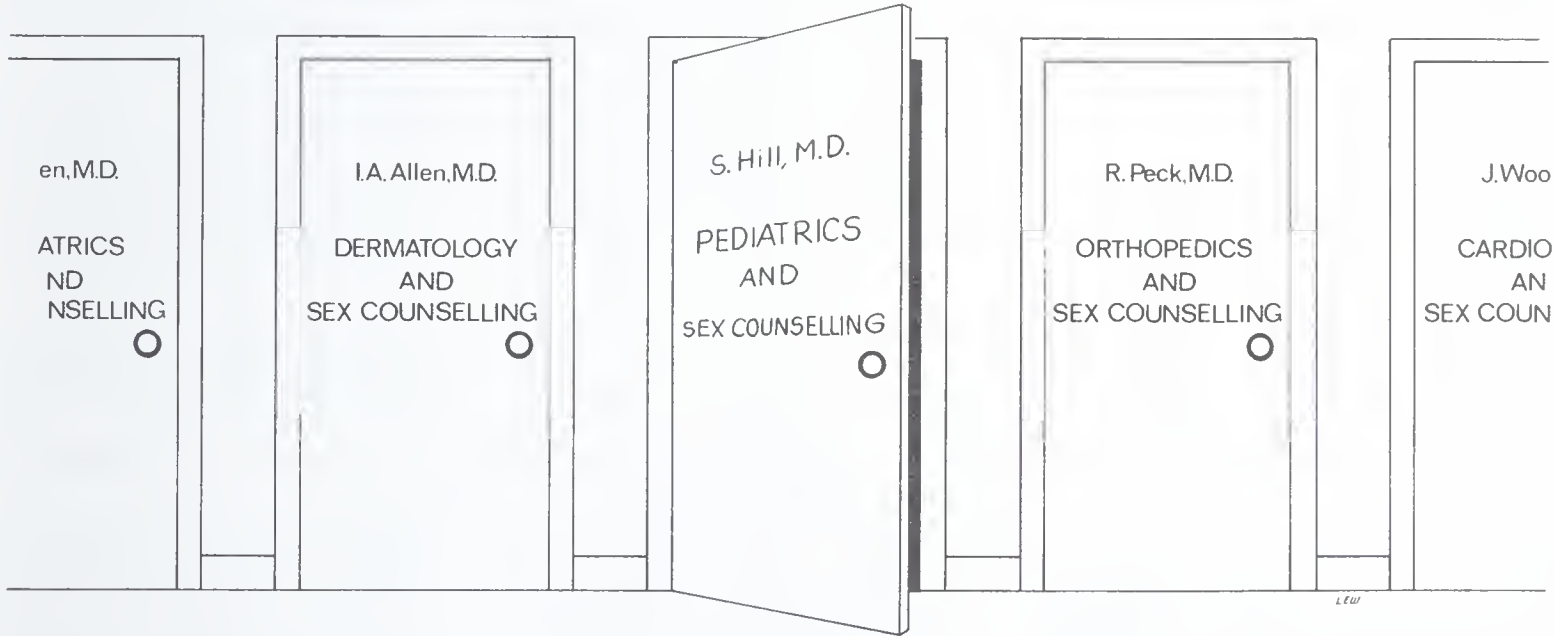
thing akin to what the States' schools have been doing for at least the last ten years. It was around four years ago that she was authorized, by what has been loosely labelled the Cinader Committee Report to the Dean, to design a sample curriculum for teaching human sexuality to medical students, and three years ago it was first introduced to first year students. The Cinader Committee Report (October 4, 1972), officially entitled "Period I, an Evaluation of Teaching in Terms of Defined Goals", in considering the frequency with which problem areas are encountered by a general practitioner, concluded that human sexuality was one of three top priority areas (the other two being human nutrition and growth and development) that deserved more extensive coverage. "Dismayed to find that normal human sexuality was dealt with only by the Behavioral Sciences, who had programmed a three hour session on that topic, (it) recommended that the 'psychodynamics of sexuality' and the physiological aspects of sex or 'normal human sexuality' should be included in the curriculum."⁶ Period I's coverage of plain old human reproduction was considered to be substantial and sufficient.

On the Skids

Here we are four years later floundering. We don't need longitudinal

teaching someone from *your* generation about sex!!" have been some of the comments elicited. Yet no one would, or could, make any positive suggestion about *how* to better teach sexuality or exactly *what* to teach. (To compound the problem, Canada apparently has nothing akin to the American Center for the Study of Sex Education in Medicine to provide direction. Our own Department of Studies in Medical Education has not gotten involved and/or interested in the problem either.) Yet, predictably, nearly everyone stuck to their guns in acknowledging the absolute importance of the subject for medical students.

So, what do the students think? A clear majority (of those who bothered to answer the end-of-course evaluation form) believed that *all* of the presentations were "very relevant" to their medical education except, inexplicably, "The Rape Offender and His Victim". (For those unfamiliar with the course, the other topics presented were Myths and Misconceptions; Biology of Sex; and Sex and Society: The Legal Implications of Sexual Behaviour; Sexual Orientation: Alternate Lifestyles; Psychosexual Development in Childhood and Adolescence; Adulthood, the Middle Years, and Later Life; Reproductive Sexual Behaviour: Contraception, Abortion, and Infertility; The Physician at Risk; Counselling the Handicapped; Female



stuff! What's happening in *Canadian* medical schools?" And *that*, my dear Nanook, is a very good question. Something is happening here, yes... but God knows what!

According to the AAMC 1975-76 Curriculum Directory, electives in human sexuality are offered at every medical school in Canada except Ottawa and Alberta. I asked Dr. Elizabeth Cape, administrator of last year's Human Sexual Behavior portion of our Behavioral Science (B.S.) requirement, *when* medical educators here in Toronto first began to try to introduce some-

studies to see that the cost-benefit ratio is heavily unbalanced: benefits to students (which would of course be passed along to patients) being negligible relative to costs. Acute dissatisfaction with what has been offered is the dominant theme of opinions on the subject. Nearly every staff member I've spoken to has proffered a pejorative view of the late Human Sexual Behavior course. "On the skids", "poorly handled", "shape up or ship out", "can't teach attitudes", "wrong emphasis" (i.e., on *dys*function rather than *eu*function), and "Imagine! Someone from *my* generation

Sexual Dysfunction; Male Sexual Dysfunction; Sex Counselling and Sex Therapy: Phew! Looks good, you say? Unfortunately, in this case, appearances are deceiving.)

In addition, most students thought that most of the above topics contributed slightly more to their *knowledge* than to a clarification of their *attitudes*. In view of the stated objectives of the course, "to help prepare the student for his/her inevitable involvement as a practicing physician with the sexual concerns of patients and their families, and concomitantly to challenging the

student to examine critically his or her own attitudes and values"⁷, one could judge it to be moderately successful, using only the questionnaire evaluation as a dipstick. But then again, just listening to students gives one rather an opposite impression—boring, irrelevant, bad timing, impersonal presentation, wrong emphases, too pie-in-the-sky, didn't learn anything, etc.

What's Cookin'

So, what's to be done? The course is currently being overhauled, to be presented to the class of 8TO and succeeding classes in their second not first year. (Perhaps the B.S. Department should actively solicit help and advice from students?) Advanced topics in sexuality, including SAR's, will be offered as well. Still, logistics (classes are too large, experienced group leaders are in short supply) as well as substance (normal vs. abnormal, sensationalism vs. ho-hum, attitudes vs. skills vs. knowledge) remain problematic. The grope-in-the-dark approach appears to remain the *modus operandi*, for lack of any better direction or model. (Perhaps I should emphasize, before continuing any farther that I'm not casting aspersions upon the B.S. Department. I don't believe that anyone else could have done any better in the circumstances. Particularly after nosing around on the subject, I can well appreciate the difficulties inherent in any attempt to actualize the stated, and very reasonable, objectives of the course.)

Nearly everyone agrees that representatives from other disciplines should participate in designing and delivering

the course (i.e., Ob-Gyn, Psychiatry, and Physical Diagnosis). Dr. Cape hopes to add a number of questions to the (in)famous Green Book of history-taking designed to elicit a sexual history from patients. "A sexual history, if nothing else, establishes an atmosphere in which a patient can feel free to discuss any problems she/he may have in sex and/or marriage."⁸

I don't pretend to have any sure-fire solutions, but it seems to me that a holistic approach to the patient should be pointedly emphasized. In addition to the sexual ramifications of organic disease, the normal interrelation of sexual and physical well-being cannot be ignored. Furthermore, there is a lot more to sex counselling than treating dysfunction. 80% of all couples presenting for sexual therapy have a significant underlying relationship problem. For the teenager, the doctor is often the only source of accurate information and advice. The demand for competent sexual counselling of the physically disabled and chronically ill exceeds the supply.

A certain propensity to see B.S. as a 'poor cousin' can only throw a wrench in the cooperative works of clinical physicians and non-physicians, and should be admitted and avoided. Perhaps combining B.S. or preceding it with some study of Ethics would also help to achieve the desired ends. To "increase awareness of different kinds of value perspectives and moral convictions that may lead to greater understanding of the apparently bizarre behaviour of patients or fellow physicians"⁹ through a consideration of Ethics would nicely complement the progress

of B.S.-induced personal attitude reassessment.

To be fair, it should also be recognized that part of the problem lies in the medical students themselves. Notoriously oriented toward hard core subjects, many students feel uneasy, or uncomfortable, or, yes, even threatened by soft core subjects. Since medicine is a people-oriented activity, students must accept the fact that people are 'fuzzy'—a black-white approach to the gray areas of medicine simply won't work.

In any event, whether we as future doctors are to be victims, survivors, or refugees of the sexual revolution depends on what's happening here and now. It would not be unseemly for us to help decide what we need to know, and demand satisfaction from the 'experts' who are paid to deliver, just as they, and our future patients for that matter, most certainly will demand a certain level of competence from us.

Next Issue: Confessions of an SAR survivor!

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... and that concludes today's lecture."

Neomorts

by

David Arnold 7T9

"Who's the new admission?"

"A young kid. Paul, I think his folks were calling him, though he'll surely not hear them."

"What's his problem?"

"Motorcycle accident. You know, over the bars then . . ." The nurse grinds her palms together simulating the impact of head on cement.

"Pretty well D.O.A. Coned before we could do anything."¹

"How old?"

"About 18."

The younger nurse, herself only 20 asks no more questions. Together, the two of them silently enter the Acute Head Injury unit where the boy lies, his brain crushed and torn. They check vital signs, pupils, the settings on the respirator, but they're busy with nothing except watching the final slide into oblivion. The neurologist is with the parents, telling them that all hope is gone; that their son is dead; that life support will be terminated. The parents say nothing. They know that when Paul's brain died, everything that was "Paul", the son, the student, the youth, died as well.

The moment of death has always escaped adequate definition. But this used not to be a major difficulty, for if the supposed corpse were left long enough it would inevitably show the classical signs of death: coldness, rigor mortis and finally, putrefaction. But the ability of modern medicine to maintain visceral function when all the higher functions that constitute 'personhood' are absent created a dilemma, for the maintained body would retain its life-like state, apparently no different from that of a person asleep. Yet there clearly is a difference.

Recognizing this difference, physicians for years practised surreptitious euthanasia when they felt that the 'life' being sustained through the grace of



the respirator was not that of a human. But the decision to withhold support or treatment so that death would occur was fraught with anxiety, guilt and not inconsiderable risk. As the feasibility of supporting the bodies of brain-dead individuals increased, many people, both within medicine and outside of it, moved to solve the dilemma of euthanasia. The solution was elegant; death would be redefined. Now, an individual in deep coma, with no reflexes, a flat EEG (for 24 hours and in the absence of hypothermia and/or CNS depressants), and no spontaneous respiration need not be *allowed* to die by removal of life support. He was dead already.

The solution was more than elegant. It was an intelligent and humane decision which acknowledged the pre-eminent position that the brain holds in any definition of humanness. So-called 'brain death' is an almost universal standard by which the status of brain-injured individuals is judged.

So Paul, the young motorcyclist, was dead, one of thousands who die in much the same way every year. Such a waste! More than just a young life has been lost. For when the respirator is turned off, the heart stops beating, the blood stops flowing. And that vigorous, tireless heart; that fertile, prolific bone marrow, that wondrous, magical machine, the liver; in fact, the entire delicate, priceless ebb and flow of life, raised to a fine art by a few chemicals are worth only a handful of dollars; all this is lost too.

Why this perverse eulogy? Because, while the new definition of death grants the right to 'pull the plug', it also implicitly grants the privilege of *not* pulling the plug. Death has occurred already; there is no need to sacrifice the body as well.

This arresting notion was brought

forward in an article entitled 'Harvesting the Dead' which appeared in the September 1974 edition of *Harper's Magazine*. The author, Dr. Willard Gaylin, outlined how the new criterion of brain death created, quite inadvertently, an entirely new resource for the advancement of medicine—cadavers with functioning bodies (except, of course, for their nervous systems)—and that the exploitation of this new resource could prove to be very rewarding.

O Tempora, O Mores! This essentially humane, decent, well-intentioned attempt to define death has produced a creature worthy of Dr. Frankenstein. Dr. Gaylin coined the term 'neomort' to describe this dead (legally) yet alive (physiologically and biochemically) creature.

And what sort of creatures are neomorts? Certainly there is no neurological function. But as long as the respirator supplies oxygen and removes carbon dioxide, the heart will be able to supply blood with its attendant nutrients to cells. A neomort is, therefore, a warm, pulsating, excreting, evacuating cadaver. Of course, they require feeding and grooming from skillful nurses and they need physiotherapy or else they'll develop bedsores or pneumonia. In fact, they would be hard to distinguish from the comatose patients who used to, and perhaps still do, reside in the wards of chronic neurological hospitals. It is important in all of this to remember that *neomorts are dead*. While it is their functioning bodies that make them attractive as resources for the advancement of medical knowledge, it is their non-living status which allows us to consider utilizing them.

To date, the dead have played an important but limited role in the advancement of medical knowledge. Post mortem examination has provided invaluable insight into the structural basis of disease. Anatomical studies are still near and dear to us. Recently, of course, the legacy of the dead has been extended to kidneys, hearts and corneas, but these are for therapeutic, and not educational use. The dead have given us what they can, but their inescapably inert nature precludes their helping us much with the dynamic processes of health and disease. In fact, it is to the living; hospital patients, mental retardates, prisoners and animals, that medical education and knowledge owes its gratitude. Now we have neomorts. Can they be of service to the living? To help your imagination unwind, here are a few possibilities:

i) Training: Routine physical examination, vaginal and rectal examinations, could be practised, sparing both the

student and the often unwitting patient the fumbling and discomfort of the first few times. Procedures such as lumbar punctures, pneumoencephalograms, cut downs, and intra-arterial catheterization could be perfected without going near a living body. And interns and residents could learn their surgery *outside* the operating room.

ii) Testing & Experimentation: The testing of new drugs is an obvious use of the neomort; the intact physiological status of many of the body systems would provide enormous amounts of useful information about the efficacy and toxicity of drugs, allowing the good ones to be brought into clinical medicine years before they would otherwise be available. But, it is as a 'diseased' preparation that the neomort may prove most useful. Can vectorcardiography detect different kinds of heart damage? We could find out by inflicting damage on the neomorts heart. Cancers could be induced so that different therapeutic approaches could be studied, especially those 'risky' ones which now both tempt us and frighten us. Retarded children have been used as culture media for hepatitis virus (which was then not culturable outside the human body) in order to try to find a cure for this pernicious disease; neomorts could spare these children

this risk to their health.

iii) Harvesting: Active hemopoetic tissue could provide an inexhaustible supply of blood as long as the neomort was properly fed. Likewise, the skin could be harvested for grafts. Antitoxins and antibodies could be manufactured by infecting the neomort with the appropriate toxin or antigen. Then there are hormones, clotting factors and so on which could be collected and stored for use.

These are some of the immediate uses to which neomorts could be put in the service of the living. But you have a sterile imagination if you cannot foresee other possible future uses. For example, women unable to carry a pregnancy to term but desirous of being mothers could 'borrow' the wombs of neomorts and have the neomort undergo the pregnancy following zygote implantation. Or, following careful matching of tissue compatibility, each of us could have an 'alter ego' neomort ready and waiting to provide substitute organs, blood and the like should we ever be unfortunate enough to require them.

But let's stop before we become too carried away with the brave new world of neomorts. Certainly, there are immediate, clear-cut advantages in their utilization; and the future is as promising



as we wish to make it. But one great hurdle must first be overcome—our society must accept them.

Advances in medicine have never been made without at least the tacit approval of society. Vesalius could not reveal the errors of Galen until the fresh air of the Renaissance blew away the dust and cobwebs that had accumulated because of a dogmatic Church. And neomorts shall not come to anything if society opposes them. The ongoing and vital role that the living have played in medical advancement has led to an evolution in human experimentation ethics that now fairly comfortably fits our modern outlook. But we have not evolved ethical principles for utilizing the dead since the Middle Ages although our concept of death has changed greatly since then. The cutting up of cadavers was highly secretive until a few decades ago and the only source of cadavers were the graves of the poor and friendless. Even to-day, cadaver dissection takes place well away from the public eye in the bowels of the Medical Sciences Building whereas human experimentation is openly advertised in the third floor halls of the Physiology Department. Neomorts are particularly distressing new comers because they bring the popular ethic of scientific progress into direct contact with something dark, primordial and inarticulated—our feelings about the dead.

Yet the reaction to the existence of neomorts need not be wholly negative. We live in a 'death-denying' society, we are told, which sentimentalizes dying and wraps the transition to death in a shroud of euphemisms. It is said that we seek refuge from the absolute certainty of death in 'group norms and actuarial statistics' and when faced with the reality of an individual death, we are likely to depersonalize the event by institutionalizing it in a hospital, surrounding it with machines and people who have no stake in the event. If these observations are indeed correct, then neomorts, lacking the gruesome reality of the cold, stiff, putrefying corpse, and attended still by nurses, doctors and machines, should find a welcome place.

Moreover, for many humanists, theologians and social thinkers, the difference between life and death is not to be found in the characteristics of corpses but rather in "the ultimate loss of consciousness, the end of all meaningful experience, the cessation of creative engagement in life, or the dissolution of personality."² It is the loss of 'personhood' rather than the loss of 'aliveness' that we mourn, and which allows us to withdraw our emotional investment. If our society can live with

the practice of sending the infirm and degenerating elderly to nursing homes when their lives become 'meaningless', 'uncreative', or when their personalities 'dissolve', then we should have little trouble accommodating the new 'nursing home' full of neomorts.

Even the altruism can be invoked in support of neomorts. The ultimate altruistic act is, of course, the conscious giving of one's life for a cause deeply believed in. Our history and literature tell of men and women who have made the ultimate sacrifice for their families, for their countries. It is an ethic that society cherishes. Giving one's body for the benefit of others after one has finished with it is clearly a less generous act. Yet it is to our altruistic selves that Kidney Societies and Eye Banks now appeal through the convenience of our Driver Licences; it is to this same altruistic self that neomort advocates could appeal with much more fervour. And the charitable act of donating one's body is highly egalitarian, with the body of a sharecropper no less worthy than that of a captain of industry. If sharing our expendable bodies in this way seems more odd than noble, perhaps it is because we have no ingrained, time-honoured tradition of altruism in this respect since until recent times, a dead body was of no value to anyone. But technology has changed all of this.

But can technology change everything? Because humanists and other social worthies feel that 'personhood' is more significant than 'aliveness', can we all embrace this elegant distinction? Because our present society is death-denying, are we all comfortable with our customs? Are we infinitely malleable?

Jung said that our personalities were erected on the framework of a transpersonal, collective unconscious, the "psychic residue of man's evolutionary development".³ What has taken thousands of years to develop in our brains will not be replaced by one generation's theories, habits or technical abilities. This is not to say that we exist in an ancestral straight-jacket unable to move in our own world. But we do have deeply felt, often irrational, anachronistic, predispositions which influence how we react to the world we find ourselves in. Dying is not new to our species. Archaeologists find the funerary relics (and little else) of bygone civilizations; and the relics reveal the ongoing ethic that dignity survives death—the body is not just garbage. Death rites addressed to the inert body have been important to the living; to allow expression of grief, to reaffirm the vitality and community of those

still alive, give voice to their awe at the process of transfiguration.

Is it the very absence of all signs of life which allows the final catharsis of the living? For centuries, humans have sought to maximize the gap between the living and the dead. Bodies were bled or allowed to putrify before burial so that none of the familiar signs of life would be present. Will a memorial service commemorating the loss of 'personhood', while the neomort lies elsewhere demonstrating all too many of the 'familiar signs of life', be a sufficient death rite? Perhaps so for our modern intellects, but will our primordial selves require more?

What is most striking when a person hears of neomorts for the first time is the unbridled repugnance that is evoked. After the benefits are clarified, however, and it is explained that no one would become a neomort against his own will, or that of his family, many dismiss their repulsion as an 'emotional', i.e. stupid, response. Yet, even when all the counter-arguments to neomorts are tidily taken care of, the repulsion remains; but it is easily discredited as a byproduct of our inadequate education and experience. Was blood transfusion not equally repelling at one time? Still, the ability to find something repulsive is a quintessentially human trait. We do a violence to ourselves if, because we don't understand its inarticulate nature, we give it.

Neomorts, like so many recent developments in medicine, are children of computers and machines. Technology, unencumbered by Feeling and loyal only to Reason marches to a rapid beat. Some people have already shrugged off the heavy burden of feelings and emotions and so can keep up; a few souls are deliberately dragging their feet, trying to slow things down; but the majority are lost and bewildered, wanting the benefits that technology promises but unsure of what the cost will be. The cost may be trivial—a matter of dollars. Or the cost might be part of our humanity. Only if we stop to listen to our inarticulate Feelings as well as to smooth talking Reason will we know.

NOTES:

1. "coned This term refers to the herniation of the brain stem through the foramen magnum resulting in severe brain stem damage. Coning results from very high or rapidly rising intracranial pressure.
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Family practitioners should probe into their patients' family lives

Pro:

While the word "probe" has a rather pejorative connotation, summoning up visions of doctors poking their noses in where they are not wanted, this function is very important. It is a physician's duty, especially one who calls himself a "family practitioner" to look after his patients' total well-being, and since their physical health is dependent upon their mental and socioeconomic health, he must be concerned about all aspects of the patients' family and business life.

There are obviously some occasions when the physician has no right to probe. Asking a new patient, who, for instance, presents with an ingrown toenail about his relationship with his boss or his spouse, or his sex life, is rightly going to be perceived as mere curiosity. As with many other things, it is not the actual situation which is important, but the patient's perception of the situation, which will determine his reaction. The doctor must gradually get to know the patient and must make evident his concern for the patient's complete health, and then his questions will be perceived as a legitimate measure of his concern, rather than as an unwarranted intrusion.

Con:

No! It is my considered opinion that doctors should not "probe" into family affairs of their patients. There should be a limit, however obscure, to the responsibilities shouldered by physicians; that limit is on the near side of getting involved in the interpersonal dynamics of a patient's life space.

When a patient walks into his family physician's office, it is the medical advice of his physician the patient is looking for and not to ask his physician to tell him how he should live his life. Nevertheless the family physician starts to retrieve information which is often irrelevant to the clinical problem under examination. In the process of taking down such irrelevant information the physician proceeds to evaluate his patient not only physically but also psychologically.

The dangers of such a practise are many fold. First the physician has taken away the rights of his patients to get only what they demand. The intentions of the patients to merely obtain a physical check-up is now extended to the evaluation of their psychological states, social relationships, intellectual abilities, etc. This is almost as ludicrous as being imposed by a salesman to buy four packages of goods, just because he decides that it would be beneficial for you, even



There are many reasons why a physician should know about his patient's family life. Firstly, patient compliance with treatment is dependent on the patient's family situation. For instance, prescribing a treatment regime that will require another person's assistance, as to an elderly person who lives alone far from close relatives, will clearly not be sufficient. The physician must make sure that assistance is made available to the patient—who in many cases would not like to "bother" anyone, but would simply fail to follow the prescribed regime. Only if the doctor is fully aware of the patient's situation can he cope with the problem.

Again, prescribing a diet to an overweight teenage girl, whose father and brothers constantly tease her about her weight and dieting, will be quite inadequate. To truly help the patient, the physician must probe into her family relationships and find some way to strengthen her interaction with her family.

Another reason for probing into the patient's family relationships is that the patient's illness may affect the family. This is especially true of chronic diseases. The physician

though you are only asking for two. The greater danger, however, is that the family physician is often not adequately trained to make such evaluations. By arbitrarily judging the mental states of his patients, in effect, the physician is taking the lives of his patients into his own hands unnecessarily, since such an evaluation not only may influence the prescription of a more effective treatment, but if the patients learn of their own diagnoses, some of them will act according to the expectations of their physician. It has been well documented that once a person has been labeled mentally ill and his environment, such as, his family has accepted the diagnosis it becomes almost impossible for him to be treated in a normal fashion again.

On a less serious scale, the physician may jeopardize his patients' equilibrium by projecting his own values and social norms into his patients' lives. For example, by advising a patient to move out of his home after having decided that the patient's cause of headache is due to his resentment towards his mother, the physician may have put his patient's life into a crisis, as well as doing the same thing to the pa-

Pro: *(continued)*

must investigate the patient's relationship with his family, and if possible should meet with members of the family. He must not only help them to take care of the patient, but also to cope with the problems and emotional strains of living with a chronically sick person. The goal must be to unite the whole family and give them all strength. Only by expressing an interest in the family, and, indeed, by probing into the patient's relationships with family and friends, can the physician be in a position to effectively treat the patient.

Finally, the family practitioner should be practising preventive care. When the housewife is brought into emergency feet first from an overdose, or the overworked businessman who drank too much to please clients hits skid row, it is too late to ask if the patient has any problems at home, at work, or in his leisure hours. The doctor has the responsibility to gradually come to know the patient, his family and his work life, while the person is still healthy. Then, if a problem does develop, the physician may be sufficiently well known and trusted by the patient to be confided in, and thus a crisis might be averted. Also, if the patient does become ill, the physician will be better equipped to deal with that illness.

The doctor-patient relationship has traditionally assumed that the physician is to be trusted to take care of all parts of the patient's body—parts that no other person would be permitted to see. Today, the doctor is expected to take care of the patient's complete health—physical and emotional. Any physician who "respected his patient's sensibilities" by refraining from a complete physical examination would be thrown out of practice—any family practitioner who neglects to examine the patient's mental and emotional health, and his family life, is acting with the same degree of irresponsibility.

Anne R. Crowe 7T9

Con: *(continued)*

tient's mother's life, who has not even come in to consult the physician's "wisdom". This illustrates the fact that by probing into the family lives of his patients, a family practitioner may very well be opening a can of worms which he has not been trained to handle and is going to make a mess of. The family practitioner would better spend his time dealing with physical illnesses which he is equipped to cope with and leave the family affairs to the family experts so that his poor patients will not have to wait for hours in the waiting room or weeks for an appointment.

What the problem really boils down to is that the family physician has given himself the right to assume the role of a moralist, and passes judgements on how his patients should live their lives. Is this because of the grandiosity of the modern medicine-man, who wants to win back some of his former influence and respect as "physician-priest"? Or perhaps the modern multi-million dollar educational system has produced doctors who are so insecure and paranoid that they have to assume responsibility and control over every aspect of their patients' lives? Or another possible explanation is that the modern physicians have overestimated their own powers and limits of the wonderful medical research and technology. Such self-appointed rights are absolutely outrageous and ridiculous. How would you like to have your patients suddenly assuming responsibilities to run your personal affairs? But, in fact, this problem is not only inherent to the medical profession; other professional people such as policemen, politicians, dentists, economists, priests, etc., also want to get into the act of telling everybody else how to live their lives. Perhaps the real blame should be placed on the whole social structure.

Whatever the cause of this problem may be, it can lead to confusion among the laymen and this makes your patients particularly vulnerable to your advice and suggestions. I grant that there are many advantages in considering a patient's family life in clinical evaluation, but the line between what you are capable of and should do as a physician and dictating someone's life can be very thin. Unless you practice with extreme caution, what you will be doing, in fact, is playing God!

Anonymous

Future topics of Blunt dissection:

Are 'gifts' from drug companies bribes?

Putting doctors on salary will result in better health care for the average Canadian.

Research money would be better spent in educating the public and providing more recreational facilities, etc. for everybody's use.

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by
Gabor Kelen

In 1964, Michael Lesch, then a student at John's Hopkins School of Medicine, and Dr. William Nyhan reported a case study⁶³ describing a disease state, which among other characteristics included a bizarre form of aggressive-compulsive self-mutilation accompanied by mental retardation, neurological dysfunction, and curiously hyperuricemic. In fact, these four symptoms came to be recognized as the cardinal features of the Lesch-Nyhan Syndrome (LNS). The disease was later shown to be a recessive X-linked inborn error of purine metabolism caused by the defective function of a single enzyme, of significance is the fact that LNS is the first instance of a reproducible stereotyped pattern of human behavior shown to be associated with a specific enzyme defect.

Clinical Features

Delivery of affected neonates is generally reported to be uneventful. No perceptible symptoms are evident at birth and development is normal for about the first year or so. The earliest clinical sign is a delay or loss of achieved development. Choreo-athetosis seeps in and is progressive and chronic. Scissoring of the lower extremities becomes prominent and eventually patients can neither sit nor stand unassisted^{46, 80}.

The self-mutilation may begin as early as the eruption of teeth. Every patient has bit their lips unless the primary teeth were removed early. Partial amputation about the fingers is not uncommon. Dislocation of the eye, face scratching and severe head-banging have also been described⁷⁵. These behaviors seem to be of a compulsive nature. Self-mutilation is not uncommon in the mentally retarded populations but is seldom in this form and usually does not involve the loss of tissue.

Ironically these children appear to be happiest and least anxious when totally

restrained. As soon as restraints are removed, they become highly anxious and irritable, often resulting in the described self-directed aggressive behavior. These children have sensations that are intact, and are not like anesthetics⁷⁶. They are in great pain while engaging in their obsessive-compulsive ritualistic behavior. All the patients are mentally retarded. Their neurological impairment is greater than their mental deficit, but I.Q. is hard to assess in view of the choreoathetosis. However it is generally placed below fifty in the severely retarded category¹⁰⁰.

LN patients have all the clinical features of gout due to the hyperuricemic condition^{55, 76}. The level of serum uric acid varies greatly but is almost consistently over 10mg/100ml^{76, 100}. When corrected for body weight, LN children show a five fold increase in serum uric acid levels compared to normals^{65, 78, 79, 80}. The serum of affected children is high from the first day of birth, but this should not be used as a diagnostic tool until the third day if the mother happens to be hyperuricemic. Two days are required to clear the effect from the system of normal neonates⁵⁵. Relatively large amounts of oxypurines (hypoxanthine and xanthine) were found in the urine of LN children and in each case hypoxanthine was predominant. The converse is true for normals. The molar ratio of hypoxanthine to xanthine for affected children is between 1.5-4.0 and for normals is between 0.3-0.9¹⁰⁷.

The secondary complications imposed by hyperuricemia are a problem in themselves. Untreated hyperuricemia can among other things lead to nephropathy and eventually renal failure. In fact this is the most frequent cause of death⁷⁶.

LNS is very rare. It is hard to estimate the number of cases presently known since mere detection of the disease is no longer documented. In 1971, 175-225

cases world wide were estimated¹⁰⁰. The disease has been found exclusively in males, but no other selectivity is evident i.e. race, religion, socio-economic level, geographic location etc. There has been at least ten cases reported in Canada. Most patients do not live to reach puberty and die of secondary complications usually associated with hyperuricemia or respiratory ailments.

Excellent and detailed reviews on the clinical features of LNS are provided elsewhere^{75, 76}.

Pathology

The research into pathology yield two routes of investigation. Firstly, the search for lesions and other causes of neurological dysfunction, and secondly, the pathological state produced by hyperuricemia.

The most consistent autopsy finding reported on LN patients then are: urate crystal deposition in the kidneys, and the absence of lesions in a mildly microcephalic but otherwise seemingly normal brain. The myelin show remarkable integrity and there are no microscopically discernable lesions in the basal ganglia⁷⁶. The pathological observations with which we are confronted, pose the following dilemma. Abnormally high uric acid levels in the blood serum and urine, (associated with the deposition of urate crystals in the kidneys and tophaceous deposits in other regions), are concomitant with the lack of evidence for urate crystal deposition in the brain or observable destructive lesions therein. This is of special interest particularly with respect to the basal ganglia which is undoubtedly involved in the neurological dysfunction manifested in LNS.

Hyperuricemia is probably unrelated to the behavioral and neurological impairment. Other hyperuricemic disease states (Gout, Glycogen storage disease Type I) do not show such disturbances.

In light of these findings, the concept of a functional lesion, as opposed to a mechanical lesion, attracted attention as being the possible source of explanation for the neurological manifestations of the syndrome.

Seegmiller, Rosenbloom and Kelley⁹³ were the first to demonstrate an apparent deficiency of the enzyme hypoxanthine guanine phosphoribosyltransferase (HGPRT) (E.C. 2.4.2.8.). Assays of HGPRT activity from liver and brain of LN patients show no detectable activity, while in controls HGPRT is highest in the basal ganglia⁸⁷. If the level of the enzyme in the brain reflects its importance for normal brain function, it should explain why the neurological manifestations associated with abnormalities of the basal ganglia predominate.

Impaired cellular proliferation might be a factor in the pathogenesis of brain damage, especially in light of microcephaly as a constituent feature. In rats, HGPRT activity of the whole brain increases rapidly during the first three weeks of postnatal life^{1,14}. The rate of brain growth of human neonates is thought to be similar to the five to ten day old rat.¹⁹ Accordingly, it is possible that HGPRT also increases rapidly during this time period for humans. Furthermore, this term coincides with the highest activity in protein and nucleic acid synthesis as well as synapse formation²⁵.

Biochemistry of Purine Metabolism

In order to realize the effect of HGPRT inactivity, purine biosynthesis will be briefly reviewed. There are several pathways involved in purine metabolism (Fig. 1) and detailed discussion is presented elsewhere^{8,26,42,49,101}.

One of the pathways and an extremely important one in our case, is that of purine synthesis *'de novo'*. Components of the purine ring are derived from formate, carbon dioxide, amide nitrogen of glutamine, amino group of aspartic acid, and glycine. Inosine-5-monophosphate (IMP), also known as inosinic acid, is the parent purine compound produced *'de novo'*. It is generally believed that this pathway is not too important in the functioning of cellular metabolism^{13,101}. IMP is chiefly used for the synthesis of adenine and guanine nucleotides, adenine-5-monophosphate (AMP), also known as adenylic acid, and guanine-5-monophosphate (GMP), also known as guanylic acid, respectively.

The first step of the *'de novo'* pathway is the rate limiting one⁵⁵. It involves the conversion of glycine, and PRPP to 5-

phosphoribosylamine by the enzyme glutamine phosphoribosyl-pyrophosphate amidotransferase. This limitation comes with the feedback inhibition of purine nucleotides AMP and GMP. These two substances can act on the 6-amino and 6-hydroxy sites of PRPP amidtransferase respectively. Since IMP is used for the synthesis of adenine and guanine nucleotides, they are usually present in sufficient quantity to keep *'de novo'* synthesis at a minimum.

In addition to *'de novo'* there are several salvage pathways that utilize intact bases which arise from prior cleavage of nucleotides. The purine bases are converted to their corresponding ribonucleotides, by reacting with 5-phosphoribosyl-1-pyrophosphate (PRPP), which acts as a substrate for their respective catalytic enzymes. Two enzymes have been identified for this process: one for adenine; adenine phosphoribosyltransferase (APRT), (E.C. 2.4.2.7); and one for hypoxanthine, and guanine; hypoxanthine guanine phosphoribosyltransferase (HGPRT).

Xanthine is also converted directly to its ribonucleotide xanthine-5-monophosphate (XMP) also known as xanthylic acid, by the same enzyme HGPRT, but the activity with xanthine is only 1% that observed for hypoxanthine and guanine⁶⁰ and consequently such a function is probably insignificant *in vivo*.

The formation of purine nucleotides inhibits their own formation. GMP further inhibits the pathways from XMP to xanthine and hypoxanthine to IMP while AMP additionally stops the formation of adenylosuccinic acid (SAMP) from IMP. The CNS is known to depend largely upon the salvage pathway.⁴⁸ It should be emphasized that uric acid is the discernable end product of the overall mechanism.

Effect of HGPRT Inactivity

As already noted, the hyperuricemic state was shown to probably result from an apparent HGPRT deficiency⁹³, three years after the documentation of the initial report.

HGPRT is normally present in all tissues of the human body and is found in its highest concentrations in the brain—particularly the basal ganglia in normal subjects.⁸⁷ It is also high in the placenta, gonads, erythrocytes, fibroblasts, and leukocytes.

The immediately noticeable characteristic of HGPRT deficient cell cultures was an increase in *'de novo'* synthesis. Rosenbloom et al.⁸⁴ examined the biochemical basis of this accelerated state. It was found that patients with LN syn-

drome incorporated up to 200 times as much radioactive glycine in their urinary uric acid as nonaffected patients^{63,66,78,84}. The existence of a causal relationship between loss of HGPRT function and the accelerated *'de novo'* biosynthesis was then sought. *In vitro* fibroblast cultures of LN patients treated with azaserine (a compound which blocks *'de novo'* synthesis at the step where amide nitrogen of glutamine is transferred to formyl glycinamide ribonucleotide (FGAR), causing an accumulation of the latter substance) revealed that FGAR accumulation was seven times as great in LN cells as in controls.^{84,85} It was concluded that excess uric acid produced was a result of increased *'de novo'* synthesis.

Later evidence showed that this increase of uric acid production was due to the conversion of IMP to AMP and further to adenosine, inosine and hypoxanthine, and from hypoxanthine to uric acid via xanthine⁹⁶. In normals, the end product is usually derived from guanine compounds by their conversion to xanthine and then to uric acid.

There are several possible mechanisms by which a deficiency of HGPRT could lead to such an excess synthesis. One of these centers around the substrate PRPP. HGPRT activity and purine biosynthesis *'de novo'* are alternative pathways of purine ribonucleotide formation. The rates of both of these processes are reciprocally controlled by competition for a common substrate, PRPP, and by inhibition from the ribonucleotide products. In normal HGPRT cells the first step in purine synthesis *'de novo'* is the rate limiting one.⁵⁵ This step requires a moiety of PRPP. If HGPRT is not in substrate competition, as is the case with HGPRT deficient cells, more substrate would be assumed to be available, thereupon a resultant increase in *'de novo'* synthesis could be speculated. In fact studies have shown that in HGPRT deficient cells four times the amount of PRPP is available^{28,40,84}. In these same studies, no increase in PRPP synthesis was observed. Originally it was concluded that increased availability of PRPP was due to decreased utilization. However the issue is now not so clear as recently increased PRPP synthetase activity due to high enzyme concentration in LN cells has been demonstrated.⁸¹

Release of feedback inhibition on *'de novo'* synthesis has also been speculated. However studies examining this hypothesis have been inconclusive,^{52,84,85} and it is thought not to play a major role.

Some related data gleaned from studying the effects of orotic acid on purine synthesis in man as well as cul-

tured cells, provide strong evidence that intracellular levels of PRPP are normally important in the regulation of purine biosynthesis 'de novo'^{53, 54}.

It has been established that AMP concentration levels are not variable between human normal and human HGPRT deficient cells. To explain this phenomenon one can refer to several studies. In human mutant hemizygote (LN patients) an increased activity of APRT was observed which enables the synthesis of adenine to AMP^{51, 93}. This increase in itself may have several reasons. Nyhan⁷⁶ postulates that a protection mechanism resulting in the diminished aging of the enzyme may be in effect, since aging is proportional to diminished activity. Alternately, this increased activity may be due to the stabilization of the enzyme by PRPP as is the case in vitro⁴⁰. This stabilization would lead to a diminished rate of degradation of the enzyme resulting in increased specific activity.

There is some evidence that the latter case is in effect. Yip et al.¹⁰⁵ purified APRT 4,000 fold from normal and LN erythrocytes. No difference could be noted in any of their tests performed, which included, neutralization by antiserum, diffusion, and immunoelectrophoresis.

The increased synthesis of adenine to AMP is consistent with the decreased adenine found in the urine of LN subjects as compared to normals⁷⁶.

Although there is an increased synthesis of AMP, as mentioned before its concentration is not variable between normal and HGPRT deficient patients. This of course could be explained by and increased utilization of AMP for the synthesis of IMP to help take up the slack resulting from HGPRT deficiency.

An interesting sideline which illustrates the extreme complexity of pinpointing the definitive pathway of purine biosynthesis and the various components involved, is exemplified by the fact that hypoxanthine and guanine supplements enhance 'de novo' synthesis in normal situations⁸⁴.

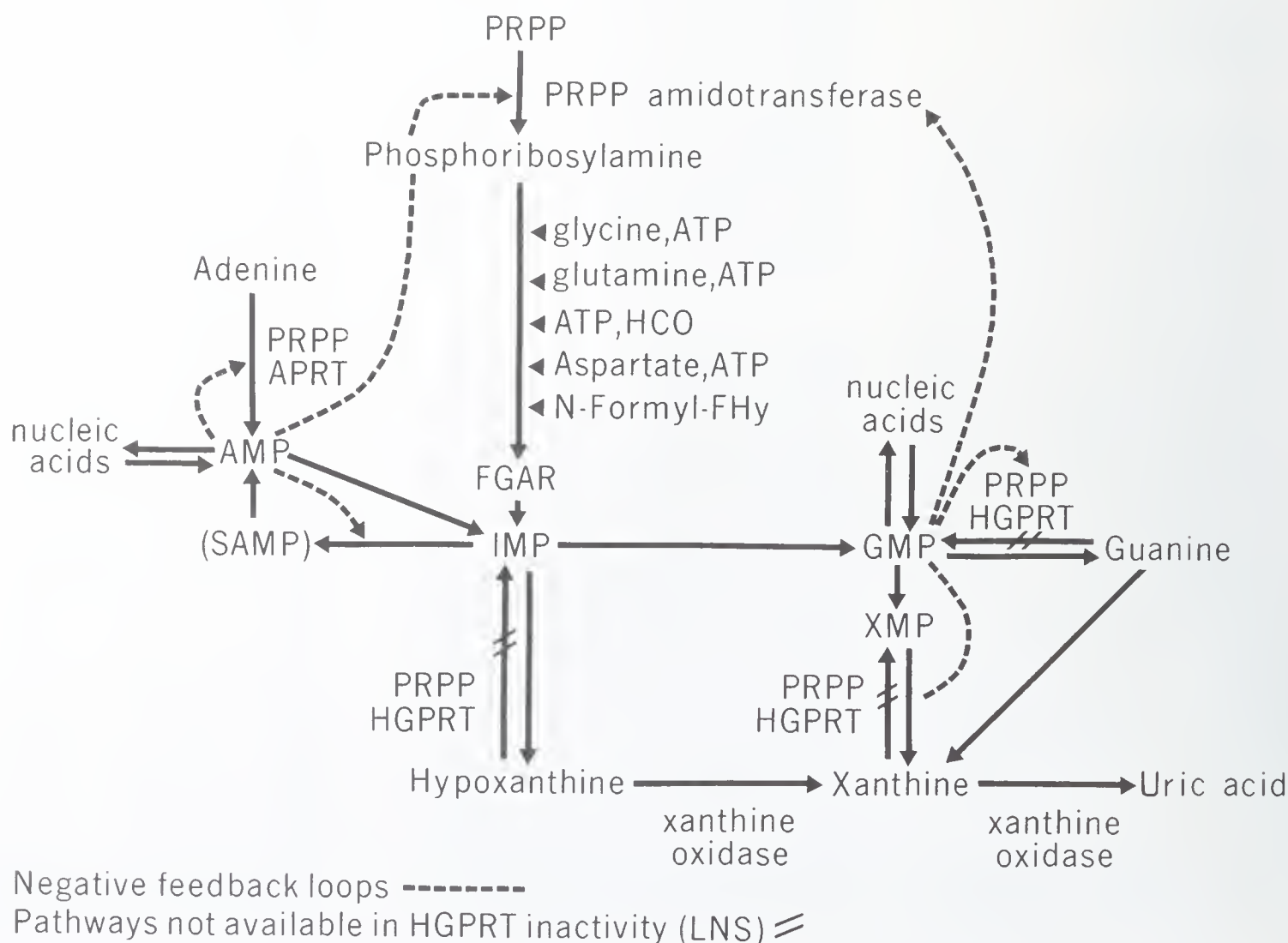
One of the big questions that come to mind is: what is the adaptational value or why does the cell increase 'de novo' synthesis to compensate for the loss of function of the enzyme HGPRT? It seems that this alternative pathway is not effectively supplying the cell with sufficient quantities of nucleic acid precursors. Further, the increase 'de novo' apparently fails to aid the cell in any known fashion.

It is possible that the 'de novo' pathway is a remnant of evolutionary development⁶⁴. One celled prototrophic organisms synthesize their own requirements from basic chemicals available in their environments. A 'de novo' purine biosynthetic pathway would be essential. As sophistication in organisms advanced, the alternative salvage pathways became more efficient and took

over the major role of producing the needed precursors required for nucleic acid synthesis, thus rendering the original 'de novo' pathway to be regulatory in function.

The etiology in some rare cases of Gout is a partially HGPRT inactive^{35, 106}. The hyperuricemic symptoms are similar but there is no CNS impairment. The interpretation of the level of enzyme activity required for no neurologic deficit is most complex and in the final analysis may prove meaningless. LN patients have been found to have enzyme activity ranging up to 7%⁶⁷. There is no correlation between degree of deficiency and severity of disorders. On the other hand, as low as .03-3% HGPRT activity has been found in gout.^{55, 59, 106} Even 0.0 activity has been reported without neurological deficit.³⁷

An animal model of self-mutilatory behaviour has been demonstrated.^{14, 90, 92} Boyd, Doleman, and Knight reported self-mutilatory behaviour in rats fed on a diet of caffeine.¹⁴ The results of the experiment are controversial since the rats were maintained on a semi-starvation diet, and the latter is known to cause an increase in uric acid concentrations, presumably due to the break-down of nucleic acids.⁴⁵ Nevertheless, it seems that caffeine (1,3,7 methyl purine) and theophylline (1,3,7 methyl purine) are effective in producing a self-mutilatory state in rats and rabbits.⁷⁶ Theophylline is the most effective



tive. Theobonine (3,7 methyl purine) is completely inactive. It seems therefore that the 1-methyl or 1,3,-methyl sites on the pure ring are important for producing this type of behaviour^{76,92}.

Recently, biogenic amines have been implicated in the abnormal behavioral aspects. Adrenergic disfunction with increased dopamine hydroxylase activity and absence pressor response to acute sympathetic stimulation was shown, in LN patients⁸³. Patients with partial HGPRT activity who were not LN did not exhibit these abnormalities. Very recently decreased MAO activity in LN skin fibroblasts has been reported¹⁵.

Pharmacotherapeutics

The initial operating hypothesis was that an over production of some purine product was responsible for the cerebral and behavioural manifestations of the disease. The fact that LN patients are normal at birth and continue to be so for the first few months lent some support for the toxic theory.

Accordingly, early therapeutic efforts were aimed at gaining control of increased uric acid levels. A logical site of therapeutic attack was the rate limiting step of 'de novo' synthesis. It was noted that in normal cells inhibition of this step was controlled by feedback from ribonucleotides⁵⁵.

Several purine analogues of hypoxanthine were investigated as possible inhibiting forces. In fact, 6-MP, 6-TG, 8-AG, and azathoprine were shown to inhibit a number of enzymes *in vivo* and *in vitro* in normal cells^{27,60}. It was thought that if these purines were converted to their ribonucleotide form in HGPRT deficient (HGPRT-) cells, these products would inhibit 'de novo' synthesis, resulting in a reduction of uric acid production.

The application of two of these analogues 6-MP and azathioprine resulted in failure.^{51,55,95} The major stumbling block was HGPRT deficiency itself. These purine analogues also require HGPRT exclusively as their catalytic enzyme. Consequently HGPRT-cells would not take up these compounds from an exogenous environment.

As a result of these studies, other purine analogues that do not require HGPRT as their converting enzyme were the focus of attention. 6-methyl-mercaptopurine (6-MMP), is converted to its ribonucleotide form not by HGPRT but by adenosine kinase⁵⁵. Administration of the drug to one patient unfortunately resulted in toxicity before the effect on purine biosynthesis could be assayed.

Another possible means of control-

ling excessive uric acid production was thought to be through a direct block within the biosynthetic pathway. The substance used here was allopurinol.

Allopurinol has the potential of inhibiting the purine biosynthetic pathway via two different sites.^{55,57,99} First it may reduce uric acid formation by inhibiting the rate limiting step 'de novo', or secondly, by acting as a competitive force for the enzyme xanthine oxidase.

In the first case there are several possible mechanisms that may inhibit 'de novo' synthesis. Allopurinol may be transformed by HGPRT catalytic action and its ribonucleotide derivative may act directly on PRPP amidotransferase. Secondly, the increased concentration of hypoxanthine that results, due to the inhibition of xanthine oxidase activity, increases the amount of IMP if HGPRT is present and this is a natural feedback inhibition of the rate limiting step. Lastly, the increase in either the hypoxanthine or IMP would deplete the tissues of their supply of PRPP thus affecting the activity of PRPP amidotransferase by directly limiting its supply of substrate.

Note that all these possibilities require HGPRT activity and are not likely to be applicable to a HGPRT deficient system. However allopurinol does inhibit xanthine oxidase and this leads to a decrease in urinary uric acid output.⁹⁸

In control and gouty subjects, the sum level of oxypurines (hypoxanthine, and xanthine) as well as uric acid levels decrease upon allopurinol administration. This oxypurine decrease is not seen in LN patients⁵⁷. In normals and those with a partial deficiency of HGPRT, the decrease can be accounted for by reutilization of hypoxanthine and xanthine. Complete absence of HGPRT makes reutilization of these oxypurines impossible, consequently these levels do not fall. In fact they increase.⁹⁸ In untreated LN patients the molar ratio of hypoxanthine to xanthine ranges from 1.5-4.0.⁹⁹ The amount of xanthine excreted by LN patients is normal, thus the increased ratio from normal (0.3-0.9) is due to an increase in hypoxanthine.^{98,99}

It could conceivably be speculated that the increased levels of oxypurines found in LN patients due to HGPRT deficiency, is responsible for the neurological dysfunction. Accordingly, allopurinol treatment might be expected to further exacerbate the severity of the neurological symptomologies because it would create a further increase in the oxypurines in the cerebrospinal fluid.⁸⁷ However no change in neurological activity was ever noted during or after such treatment.^{18,56} This indicates two significant facts. Assuming that the

neurological dysfunction is not static we may infer that the said dysfunction is due neither to elevated uric acid levels, nor to elevated oxypurine levels. Adding weight to this conclusion is the fact that abnormalities in hypoxanthine and xanthine production of a magnitude similar to that found in LN disease may be tolerated in the absence of the characteristic neurological disease.

It may be argued, that the above does not offer conclusive proof, since these studies do not include a developmental investigation of a longititude nature, on the effects of this drug with respect to neurological dysfunction. It may be that the treatment has an impeding effect on the onset of such symptoms.

A study by Marks *et al.*⁶⁶ offered conclusive proof that allopurinol has no effect on neurological dysfunction. Allopurinol was administered to a LN neonate 72 hours after birth. At that time the uric acid level was 14.5mg/100ml. By the second day of treatment the level fell to 5.1mg/100ml. The neurological development or lack of it and the automutilation in this patient was described as being the same as reported for cases without any treatment whatsoever.

Although allopurinol does not seem to influence the neurological manifestations of the Lesch-Nyhan syndrome, its importance for causing a decrease in uric acid production should not be overlooked.

Another possible means of treatment originates from a study by Felix *et al.* They found that HGPRT-strains require fifty times more folic acid than normal cells to proliferate in their medium. Adenine is normally required in the exogenous environment of LN cells^{21,28} but can be obviated by folic acid. Recently Benke *et al.*¹¹ tried such therapeutic measures on LN twins. One was administered adenine, and both were given folic acid with monosodium glutamate (MSG). Both children had delayed neurological development at about four years of age, but the severity was less than that observed for 15 affected maternal cousins. The data is difficult to interpret since much variation has been reported even in families.^{46,66,75,80}

Of special interest now is a Japanese report, which claims 4 cases of relief of self-mutilation by oral administration of 1-5-hydroxytryptophan (1-5-HTP).⁷³ No side effects were evident. No effect on choreoathetoid movements were seen.

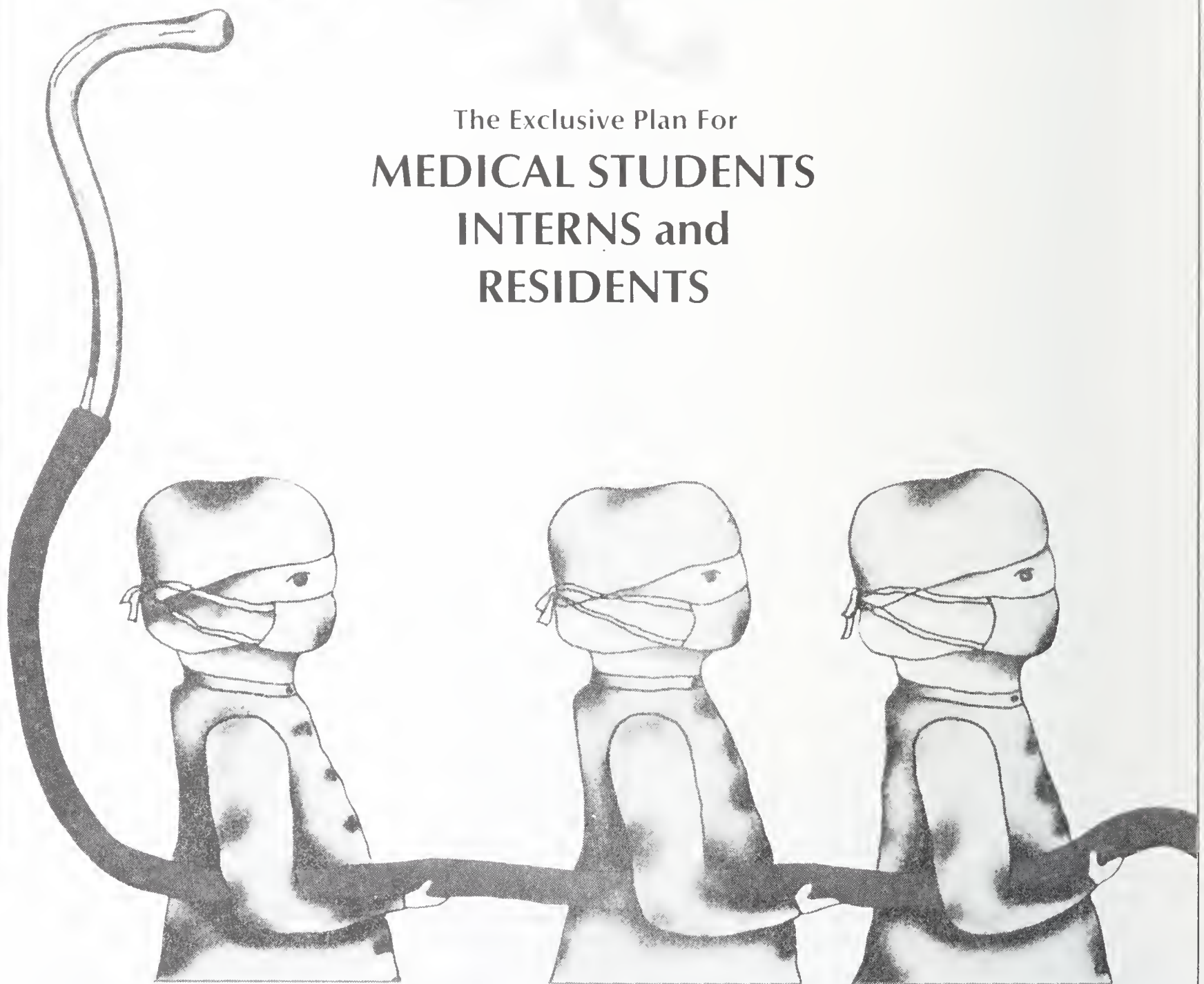
Reports claiming successful treatment of the behavioural manifestations of LNS and others like it are often difficult to interpret due to a disregard for behaviour at controls, and often a lack of understanding about them.

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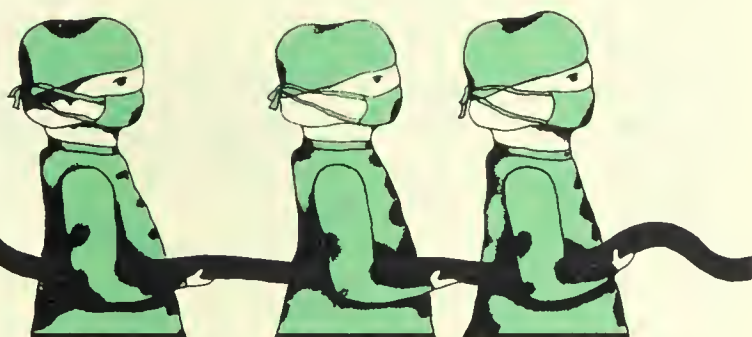
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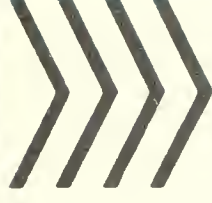
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Although it may be unrelated, 1-5-HTP has also successfully alleviated aggressive behavior in rats (mouse-killing).²³ The issue of HGPRT was not involved here.

Genetics

The first evidence that LNS was inherited in an X-linked recessive manner came from pedigree analysis.⁷⁵

A study by Henderson *et al.*⁴⁶ experimentally confirmed the conclusion of others that the Lesch-Nyhan syndrome is inherited in an X-linked manner. Analysis of HGPRT activity in erythrocytes obtained from a family with Lesch-Nyhan syndrome history, and a family with a history of gout, revealed a distribution of HGPRT activity in each family which was compatible with X-linked recessive inheritance.

Recently Shawn and Brown were able to assign HGPRT and G6PD to the distal half of the long arm of the X-chromosome and suggested the following sequence from the centromere: PGK, HGPRT, G6PD.⁹⁴

Detection of the Heterozygote

The fastest, easiest, least expensive, and still the method of choice today, makes use of enzyme assays of isolated hair follicles^{36,39}. Hair follicles apparently display a certain degree of clonal growth. A hair follicle develops from a small number of precursor cells, therefore they are not distributed at random. This increases the probability that a follicle has only one type of X-linked allele expression. This would be expected if the 'like begets like' hypothesis were in action. Apparently only 20-30 follicles need be looked at.

Three types of follicles become evident in LN heterozygotes. There are those that are deficient HGPRT, those that show normal HGPRT activity, and those that show intermediate activity. A study by Goldstein *et al.* (39) showed how this could be. An LN heterozygote, heterozygous for G6PD as well, provided the answer. The cells that had intermediate HGPRT activity, also contained both isoenzymes of G6PD, i.e. G6PD^a, and G6PD^b. This would suggest that the gene loci for G6PD and HGPRT are located in a 'cis' position in relation to each other on the X-chromosomes. Two loci that are in the 'cis' position are on the same chromosome, and both are either being expressed or both are not.

There are some problems with the hair follicle method also. It is not always possible to use on long fine easily breakable hair (78). For these females other techniques have to be used. Follicles with little or no sheath could be misclassified as mutant since HGPRT is restricted mostly to the sheath (38).

Prenatal and Perinatal Diagnosis of the Lesch-Nyhan Syndrome

Prenatal diagnosis is possible by two methods. One is based on the incorporation of tritiated hypoxanthine into nucleic acids in cultured cells obtained by amniocentesis^{16,25}. The other is based on enzyme assay on the cultured amniotic cells.²¹

Now a rapid prenatal ultramicrochemical method, able to detect enzyme activity at the single cell level has been developed.⁴⁷

After birth, male infants at risk for the disease could be detected on the basis of their deviated urinary uric acid to creatinine ratios.⁴⁰. HGPRT deficient subjects have a ratio of 3-4 mg of uric acid/mg of creatinine, while for normals it is less than 1.⁵⁰ Screening programs based on this principle have now been initiated by the Province of Quebec.⁶⁹

Two other screening tests based on erythrocyte enzyme assay are also available. One is the incorporation of tritiated hypoxanthine into erythrocytes (or rather the lack of it)¹² and the other makes use of the fact that lanthium chloride causes the nucleotide product of HGPRT to precipitate out.⁷

One other method has been proposed by Frost *et al.*³³ It is a diagnosis *in vivo*. Autoradiographs are taken of skin biopsies after intradermal injection of tritiated guanine and tritiated adenine. LN patients incorporate H³-adenine only while controls take in both. The same results are derived for skin biopsy specimens of neonatal foreskin.

Enzyme Heterogeneity

Some levels of HGPRT can be detected in some patients with classic LNS.^{34,56,96} Researchers sought the nature of the enzyme defect.

Arnold and Kelley were able to purify the enzyme HGPRT and examine its subunit structure.³ Purification of the enzyme suggested heterogeneity i.e. slightly different forms of the same active enzyme, for electrophoresis produced three peaks (isoelectric foci) for normal erythrocyte HGPRT. The findings suggest that electrophoretic heterogeneity, at least for the normal enzyme is due to a non-genetic alteration of the protein.

The nature of LN mutation which also produces heterogeneous variants of a mutant enzyme does not appear to be non-genetic. Various different mutant LN forms of the enzyme exist that are different from each other as well as normal HGPRT with respect to: heat lability, stability kinetic properties, electrophoretic migration, and sensitivity to product inhibition.^{4,5,10,52,56,68,82}

Rubin *et al* shed much light on the nature of the mutation.⁸⁸ Purified HGPRT was isolated from normal human erythrocytes and antibodies to it prepared in rats and rabbits. The antisera was used to detect the presence of an altered HGPRT enzyme in the erythrocytes of five LN patients. Results indicated the presence of normal amounts of immunologically identifiable, but catalytically incompetent enzyme.

This suggests that the mutation responsible for LN disease is a single point mutation in the structural gene coding for HGPRT causing a change in a single amino acid. Findings dispel the probability that the mutation was caused by a large deletion, frame shift, nonsense mutation or a mutation in a regulatory gene.

However the problem is not a simple one, and different types of mutations may cause the same apparent disease as was shown by Richardson *et al.* They recently reported heterogeneity of LN HGPRT in two unrelated patients. Erythrocytes from one show a 0.1% activity while the other shows 0.005%. The enzyme that was 0.1% active, was normal in all respects except stability. This is indicative of a biochemical lesion in the protein structure that does not involve the active site. The enzyme displaying 0.005% activity was altered in every characteristic. It would seem that the active site is involved. Consequently, one may conclude that different mutations on the gene coding for HGPRT leads to different mutations with the same end results, but the mutation responsible may not be the same in any two cases.

Mutant isoenzymes have also been found for partially deficient subjects who have gout⁵.

Future Therapy

Much research is now progressing toward rendering HGPRT cells HGPRT+ especially through techniques of somatic cell hybridization and chromosome pulverization. I will not dwell on these experiments except for one illustration. Wullems *et al.* have recently shown that HGPRT+ is expressed in HGPRT chinese hamster cells following incorporation of human chromosomal material.

Even if a successful *in vivo* method is eventually obtained, the picture for LNS is very complex. There is no evidence at this time to suggest that the disease process is reversible. Indeed as pointed out it may start '*in utero*'.

Perhaps genetic therapy will have to start with the heterozygous carrier.

A detail list of the references is available from the editors on request.

BOOK REVIEWS

Colour Atlas and Textbook of Macro-pathology (2nd Edition)
by W. Sandritter and C. Thomas (Univ. of Freiberg, Germany)
Translated by W. H. Kirsten
361 pages 680 illustrations, 639 colour
PRICE: \$37.95

The breath-taking beauty of some 3¾" x 2½" glossies of someone's syphilitic aorta are now yours to behold within the comfort and security of your own home! The colourful collection of photos in this atlas and textbook of general gross pathology are truly amongst the most well presented that one can find.

A certain distance (or ambivalence) is the position of the onlooker towards the use of black and white pathology specimens; they lack the dynamism and playfulness of the cacaphony of colour

captured herein. Even the authors are touched by this fancy. Next to an agglutination thrombus in the jugular vein is a view of the sand dunes of Grand Canary Island! Although this is the only digression from the subject at hand, the whole book seems to express a delight in colour and form, even if, regrettably enough, at the expense of the poor unfortunates whose organs are depicted.

Examples of many major areas of pathology have been included and thankfully, most of the obscure variety excluded... almost. (Tracheopathia osteoplastica, a rare congenital malformation consisting of plaque-like intrusions into the lumen, was probably deemed necessary for inclusion on account of its discovery on May 24th, 1909, in the Department of Pathology at the University of Freiberg.)

Clearly here we have coffee table

fare. The text is well written, precise, and pithy. To use this as a primary textbook of pathology could, however, be criminal. The clinical correlation between pathology and patient is minimal. This book is meant more for pathologists than medical students in that the text tends to be descriptive of the gross morphology serving to draw attention to the salient features of the pictures, and generalize from there to the particular pathology of the condition. On occasion, the histology, pathophysiology, or clinical correlates are covered, and when they are, they are tossed off in a few words.

Here, essentially, one has an atlas of gross pathology of use to those wishing to augment a more general textbook of pathology with a very excellently illustrated and descriptive guide to gross pathology.

Charles Krieger 7T8

FEEDBACK

I just thought I would drop you a note to compliment you on this year's first issue of the Journal... it's at least a 300% improvement over last year's... the cover design, the articles, titles and type-set—all gold stars.

Andy Kennedy 7T9

The Journal this year is a definite improvement in the right direction. However, I would still like to see more articles, shorter articles, and more artwork. Keep up the good work.

Michael

For once I actually *enjoyed* reading the Journal!

Anonymous

Re: The Feedback survey—I just wanted to say that I was shocked to see that 7% of the people who answered your survey were what you might call androgynous!. What's the world coming to?!

Anonymous

The cover is much better looking than last year's.

Second Year

I noticed some great expanses of blank paper in your first issue and am wondering why they couldn't at least have been filled with some ads, considering the Medical Society needs all the money it can get!

Money Conscious

Re: The Interview with Rakoff—a fine article. One correction, however. Julius Wagner von Jauregg (*not* Jaurich) was an Austrian neuropsychiatrist noted for his research on cretinism and for treatment of dementia paralytica by malarial infection. He won the Nobel Prize in Medicine in 1927.

Anonymous

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- a substantial allowance for the initial purchase of uniforms;
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